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During the past year (20 months instead of 12 months due to extensions) the following work has been completed:

1. Development of higher dose pyridostigmine bromide extended release tablets at doses of 90, 120, and 150 mg.
2. Formulation and production of a batch (approximately 2200 tablets) of 90 mg extended release pyridostigmine bromide tablets.
3. Characterize the physicochemical properties of aprophen hydrochloride.
4. Formulation and production of 5 mg, 15 mg and placebo WR6026 dihydrochloride capsules in batch sizes of approximately 2500 (5 mg and 15 mg) and approximately 2800 (placebo).
5. Formulation and production of 5 mg, 15 mg and placebo WR238,605 capsules in batch sizes of approximately 3000 (5 mg and 15 mg) and approximately 6000 (placebo).

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FOREWORD

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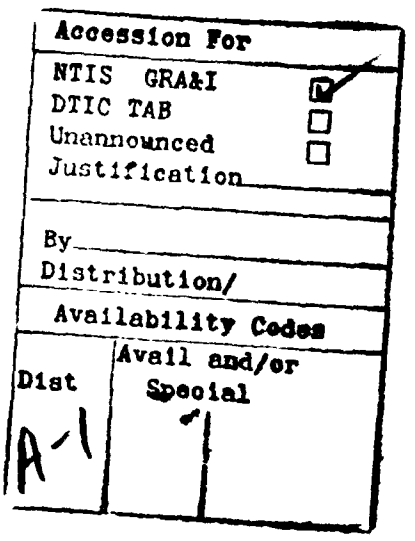

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Summary

Pyridostigmine Br extended release tablet formulations were prepared in 90 mg, 120 mg and 150 mg strengths and their release characteristics studied in vitro.

Formulations were prepared with various grades of hydroxypropylmethylcellulose (Methocel® K4M, K15M or K100M), hydrogenated castor oil (Castorwax®), polyvinylpyrrolidone (PVP, Povidone®, Plasdone® or Kollidon®) and other excipients. Extended release over 6-12 hours was desired from such formulations. Release characteristics were evaluated in vitro with the USP XXI basket method in simulated gastric fluid without pepsin.

Several promising formulations were developed which give release profiles that approximate the desired release characteristics.

Objective

Previously, extended release tablets containing 10 mg, 22 mg and 45 mg of pyridostigmine bromide were developed for clinical evaluation. It was deemed desirable to develop similar extended release formulations at dosage levels of 90 mg, 120 mg and 150 mg. These formulations were intended to release over 6-12 hours and produce sustained blood levels of pyridostigmine.

Formulation Strategy

Since hydroxypropylmethylcellulose (HPMC) and hydrogenated castor oil (Castorwax®)/polyvinylpyrolidone (PVP) had been used to produce extended release formulations of pyridostigmine Br in 10 mg, 22 mg and 45 mg strengths, these same excipients were again employed for higher strength formulations. Previously, Methocel® K4M was the commercial form of HPMC employed for 10 mg and 22 mg extended release tablets. It slows the release of pyridostigmine by hydrating in aqueous solutions and producing a viscous hydrated matrix through which the drug must diffuse to be released. Castorwax® pyridostigmine tablets were produced in 45 mg strengths. Such wax matrix formulations present a porous inert barrier through which release medium must diffuse to dissolve the drug and then the drug solution must diffuse out through the matrix. Each formulation approach is a different release mechanism for slowing the release of the highly water soluble pyridostigmine bromide.

The major concern in developing higher strength extended release formulations was the ultimate size of the final tablet. The HPMC formulations containing 10 or 22 mg of pyridostigmine weighed either 350 mg or 450 mg. Proportional increases in tablet size for 90-150 mg strength tablets would give formulations that were well over one gram in total weight. Similarly, the 45 mg tablets containing Castorwax® weighed 375 mg. A 90 mg tablet could be prepared at a total weight of 750 mg but 120 mg and 150 mg strengths would be prohibitively large. Thus, the release of higher strength tablets would have to be controlled without proportional increases in total tablet weight.

Excipients Employed

Methocel® K4M	conforms to USP XXI requirements for Hydroxypropyl Methylcellulose; K4M denotes a viscosity of 4000 cps for a 2% aqueous solution
Methocel® K15M	as above for Methocel® K4M; K15M denotes a viscosity of 15,000 cps for a 2% aqueous solution
Methocel® K100M	as above for Methocel® K4M; K100M denotes a viscosity of 100,000 cps for a 2% aqueous solution
Castorwax®	conforms to NF XVI requirements for Hydrogenated Castor Oil; waxy material with a melting point of 85-88°C
PVP K30	conforms to USP XXI requirements for Povidone; K30 is a water soluble polymer with a molecular weight of ~25,000; increases tablet hardness
Dicalcium Phosphate	conforms to USP XXI requirements for Dibasic Calcium Phosphate; improves tablet hardness and improves flow of powdered granulation
Mag. Stearate	conforms to NF XVI requirements for Magnesium Stearate; tablet lubricant
Avicel®	conforms to NF XVI requirements for Microcrystalline Cellulose; increases tablet hardness
Cab-O-Sil®	conforms to NF XVI requirements for Colloidal Silicon Dioxide; increases flow properties of powdered granulation
Cab-O-Sil® 720	hydrophobic (nonpolar) grade of Cab-O-Sil which does not wet or disperse in water

Tablet Preparation

All components (drug and excipients) were thoroughly mixed as powders by geometric dilution and then tumbled end-over-end in a screw cap culture tube for 15-30 minutes. An accurately weighed portion of the powdered blend was compressed into disk-shaped tablets at 15,000 lbs total force (11,300 psi) with a 13 mm punch and die system. Compression was performed on a Pasadena hydraulic press for one minute. The compressed tablet was carefully pushed from the die and stored in a dessicator.

Dissolution Test

At least two tablets of each formulation were tested using the USP XXI procedure (Apparatus 1, pp. 1243-1244). A stirring speed for the basket of 100 rpm, 900 ml of simulated gastric fluid (pp. 1424, USP XXI) without pepsin and a bath temperature of 37°C were employed. Samples (10 ml) of the dissolution were periodically removed for assay and the sample volume replaced with fresh dissolution medium. Pyridostigmine content in dissolution samples was assayed by UV spectrophotometry at 269 mm on a Hewlett-Packard diode array spectrophotometer. Pyridostigmine Br standards were prepared and assayed with each batch of samples assayed and a standard calibration curve calculated.

Results

Tables IA and IB contain the release data and formulation specifications for three 90 mg pyridostigmine tablet formulations containing various levels of Methocel® K4M and dicalcium phosphate. Figure 1 shows the release profiles for these three formulations. These approximate the profiles of previous extended release formulations which release over 6 hours. It did not seem feasible to achieve 12 hour release with Methocel® K4M.

Higher viscosity grades of HPMC (Methocel® K15M and K100M) were employed in six further 90 mg tablet formulations. Their release data and formulation specifications are given in Tables IIA and IIB. Their release profiles are shown in Figure 2. Tablets containing Methocel® K15M (W-4-90) released quite slowly and could be expected to release over 12 hours. Formulations W-9-90 and W-13-90 appear to follow the release characteristics of W-4-90 but their release was only studied over 4-6 hours. Tablets containing Methocel® K100M (W-6-90) or K100M in combination with K15M released very quickly. Apparently the higher viscosity K100M does not hydrate fast enough to appreciably slow pyridostigmine release. K15M in combination with dicalcium phosphate, Avicel®, etc. (W-15-90) released too quickly. This formulation corresponds to those produced previously in 10 mg and 22 mg strengths with K15M replacing K4M. Formulation W-4-90 may be satisfactory for 12 hour release but will be too soft or friable to coat without hardness enhancing excipients like dicalcium phosphate and Avicel®. Formulations W-6-90 and W-7-90 would be satisfactory for 6 hour release but they too would be quite soft.

Table IA

Percent Released from 90 mg Pyridostigmine Br Extended Release Tablet Formulations Containing Methocel K4M[a]

	Percent Dissolved		
Time(hrs)	W-1-90[b]	W-2-90[b]	W-3-90[b]
0.5	30.2(2.5)[c]	30.3(1.9)[c]	37.7(0.9)[c]
1.0	43.6(3.0)	41.5(1.7)	49.6(1.8)
2.0	59.9(0.7)	56.6(1.2)	65.2(2.7)
4.0	77.6(1.4)	75.5(0.5)	82.7(1.5)
6.0	87.0(2.8)	85.6(1.4)	91.9(0.5)
8.0	90.7(0.9)	91.6(1.1)	96.7(0.3)
10.0	92.5(0.7)	95.5(0.3)	99.4(1.2)
12.0	93.9(0.2)	97.8(0.3)	101.2(1.7)

[a]Normalized for theoretical content of 90 mg; Average of 2 tablets
[b]Formulation number
[c]Standard deviation

Table IB

90 mg Pyridostigmine Br Extended Release Formulations Containing Methocel® K4M

Component	W-1-90[d]	W-2-90[d]	W-3-90[d]
Pyridostigmine Br	90[e]	90[e]	90[e]
Methocel® K4M	250	350	300
Dicalcium Phosphate	100	-	50
Mag. Stearate	5	5	5
Total Weight (mg)	445	445	445

[d]Formulation number
[e]Weight in milligrams

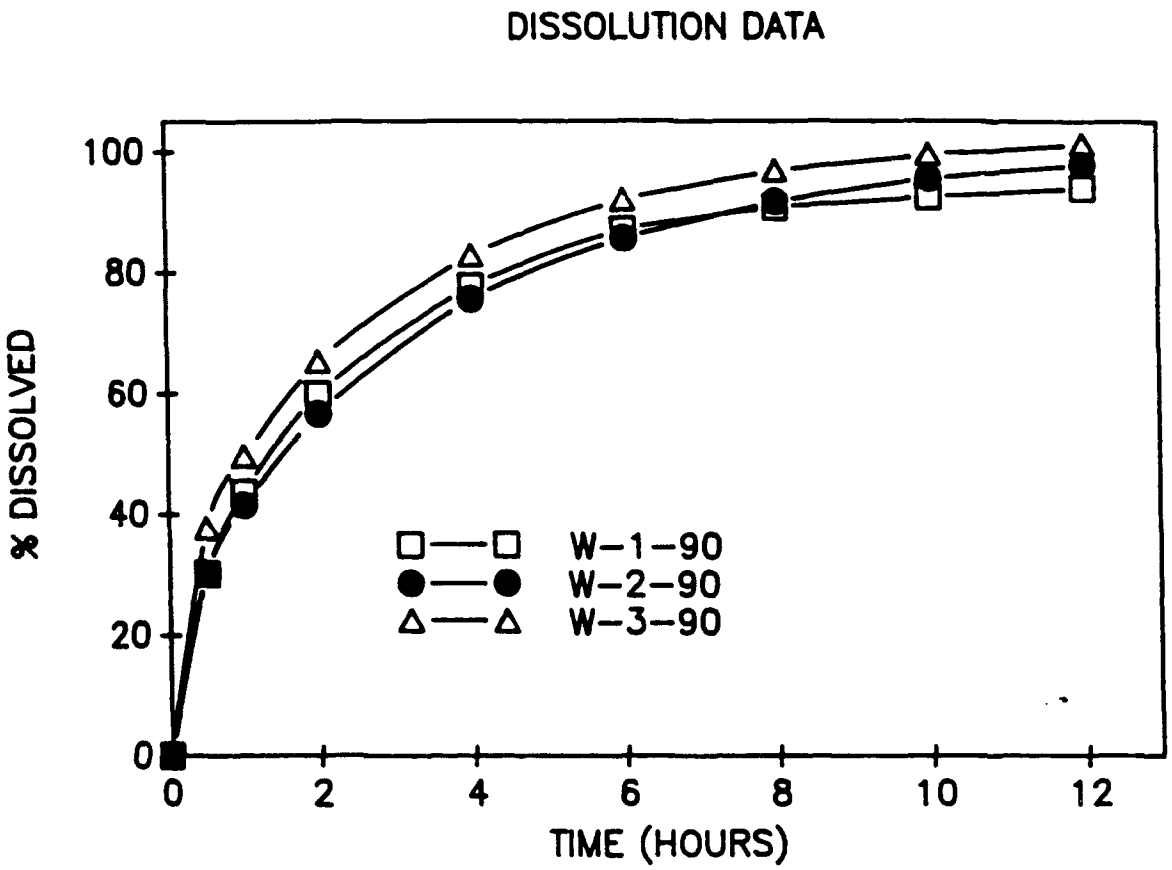

Figure 1. Release profiles from 90 mg extended release pyridostigmine Br tablets containing Methocel® K4M.

Tables IIIA and IIIB show the release data and formulation specifications for five 90 mg tablet formulations employing Castorwax® with and without Methocel® K15M. Figure 3 shows their release profiles. PVP (K-30) was added to two formulations (W-12-90 and W-14-90) to increase hardness. Castorwax alone (W-11-90) or in combination with PVP (W-12-90 and W-14-90) greatly slowed pyridostigmine release. Since formulations W-11-90 and W-12-90 released less than 100% of their theoretical content in 12 hours, their content analysis was determined to check whether they contained 90 mg. Formulation W-11-90 gave contents of 90.8 mg and 91.3 mg when two separate tablets were assayed. Formulation W-12-90 gave contents of 92.5 mg and 91.2 mg for duplicate analyses. Formulation W-14-90 has twice the total weight as W-12-90 and yet the release profiles are nearly identical. For disk-shaped tablets, increase in tablet size with increasing amounts of excipients does not appear to have much effect on release rate. Formulation W-8-90 approximates release desired for a 6 hour extended release formulation. Formulation W-10-90 appears to release similarly to W-8-90 but its release was only studied for 1 hour.

Tables IVA and IVB contain the release data and formulation specifications for three 120 mg pyridostigmine tablet formulations. Figure 4 shows their release profiles. Formulation W-1-120 has a very slow release but W-2-120 with less Castorwax® and less total weight releases faster. Since formulation W-1-120 released less than 100% of its theoretical content in 12 hours, content analysis was determined on two tablets. Duplicate analysis gave contents of 122.2 mg and 120.9 mg. An ideal 12 hour release could be achieved by a formulation of intermediate composition between W-1-120 and W-2-120. Formulation W-3-120 is too fast for 6 hour release. A better 6 hour release profile could be achieved by reducing the dicalcium phosphate and Avicel® in W-3-120 but the tablet will also become softer.

Tables VA and VB contain the release data and formulation specifications for three 150 mg pyridostigmine tablet formulations. Figure 5 shows their release profiles. Formulation W-1-150 releases quite slowly. Its release rate could be raised by decreasing the Castorwax® content. Formulation W-3-150 approximates desired 6 hour release behavior even though release in the first 0.5 hour is somewhat high.

Table IIA

Percent Released from 90 mg Pyridostigmine Br Extended Release Tablet Formulations Containing Methocel® K15M and/or Methocel® K100M[a]

	Percent Dissolved					
Time(hrs)	W-4-90[b]	W-6-90[b]	W-7-90[b]	W-9-90[b]	W-13-90[b]	W-15-90[b]
0.5	26.5(4.2)[c]	44.8(2.8)[c]	39.4(1.3)[c]	22.4(0.8)[c]	22.49(.06)[c]	42.9(0.8)[c]
1.0	35.9(5.1)	70.1(1.9)	55.1(0.8)	33.4(1.4)	32.08(.72)	69.4(0.7)
2.0	46.1(6.6)	76.9(1.9)	74.9(1.3)	48.5(1.0)	46.41(1.74)	89.8(3.3)
4.0	63.7(6.4)	92.4(2.1)	93.0(1.6)	67.1(1.2)	64.52(1.48)	102.5(0.5)
6.0	69.1(7.5)		102.5(1.7)		76.40(1.26)	
8.0	75.6(6.4)					
10.0	80.1(5.1)					
12.0	83.4(4.3)					

[a]Normalized for theoretical content of 90 mg; Average of 2 tablets
[b]Formulation number
[c]Standard deviation

Table IIB

90 mg Pyridostigmine Br Extended Release Formulations Containing Methocel® K15M and/or Methocel® K100M

Component	W-4-90[d]	W-6-90[d]	W-7-90[d]	W-9-90[d]	W-13-90[d]	W-15-90[d]
Pyridostigmine Br	90[e]	90[e]	90[e]	90[e]	90[e]	90[e]
Methocel® K15M	350	-	175	262.5	500	200
Methocel® K100M[f]	-	350	175	-	-	-
Cab-O-Sil®(720)[f]	-	-	-	87.5	-	-
Mag. Stearate	5	5	5	5	5	1.25
Dicalcium Phosphate	-	-	-	-	-	100
Avicel®	-	-	-	-	-	50
Cab-O-Sil®	-	-	-	-	-	0.75
Total Weight (mg)	445	445	445	445	593	442

[d]Formulation number
[e]Weight in milligrams
[f]Hydrophobic grade of Cab-O-Sil®

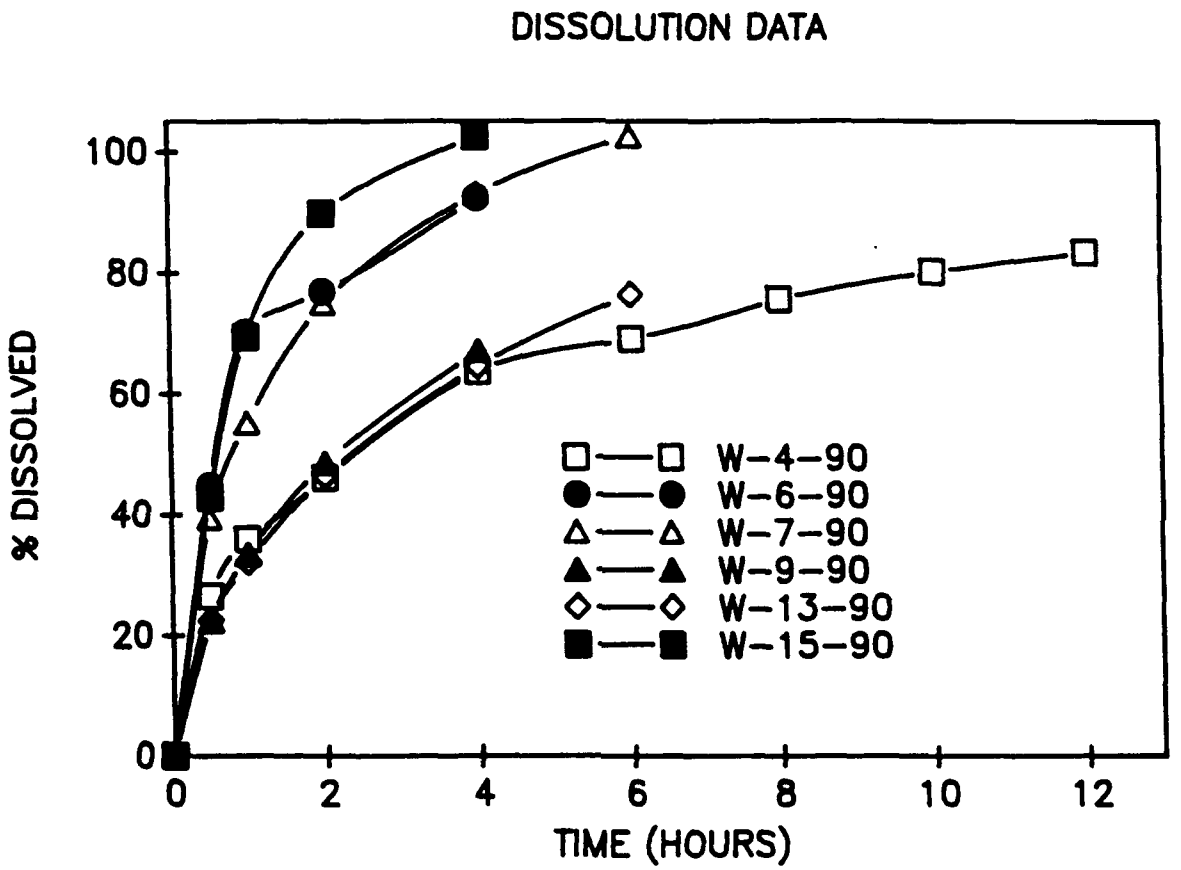

Figure 2. Release profiles from 90 mg extended release pyridostigmine Br tablets containing Methocel® K15M and/or Methocel® K100M.

Table IIIA

Percent Released from 90 mg Pyridostigmine Br Extended Release Tablet Formulations Containing Castorwax® and/or Methocel® K15M[a]

	Percent Dissolved				
Time(hrs)	W-8-90[b]	W-10-90[b]	W-11-90[b]	W-12-90[b]	W-14-90[b]
0.5	39.9(3.2)[c]	33.9(3.9)[c]	17.3(1.0)[c]	18.5(2.8)[c]	20.1(0.2)[c]
1.0	54.3(3.4)	55.2(3.9)	25.8(2.1)	26.2(4.0)	28.7(0.6)
2.0	72.9(2.4)		34.6(3.9)	37.9(5.8)	39.9(0.5)
4.0	91.6(1.2)		47.6 (7.1)	54.2(8.3)	54.6(0.8)
6.0	101.9(1.7)		57.3(9.6)	65.5(9.3)	64.6(0.7)
8.0			66.2(9.6)	73.3(9.9)	72.0(0.6)
10.0			75.1(11.7)	82.0(11.1)	78.0(0.6)
12.0			78.3(11.8)	87.4(10.9)	83.6(0.0)

[a]Normalized for theoretical content of 90 mg; Average of 2 tablets (W-8-90, W-10-90, W-11-90 and W-14-90); Average of 4 tablets (W-12-90)
[b]Formulation number
[c]Standard deviation

Table IIIB

90 mg Pyridostigmine Br Extended Release Formulations Containing Castorwax® and/or Methocel® K15M

Component	W-8-90[d]	W-10-90[d]	W-11-90[d]	W-12-90[d]	W-14-90[d]
Pyridostigmine Br	90[e]	90[e]	90[e]	90[e]	90[e]
Methocel® K15M	262.5	87.5	-	-	-
Castorwax®	87.5	262.5	350	250	500
PVP (K-30)	-	-	-	30	150
Mag. Stearate	5	5	5	5	10
Total Weight (mg)	445	445	445	375	750

[d]Formulation number
[e]Weight in milligrams

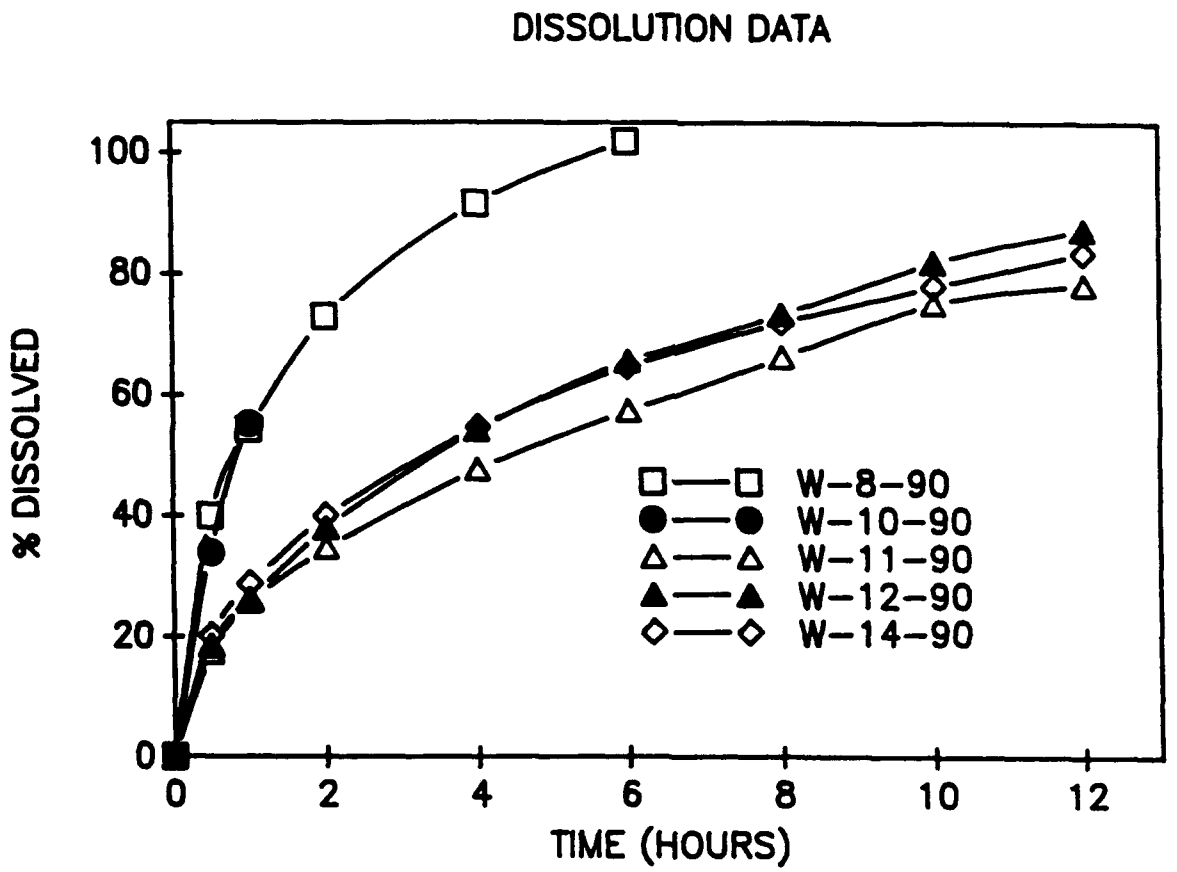

Figure 3. Release profiles from 90 mg extended release pyridostigmine Br tablets containing Castorwax® and/or Methocel® K15M.

Table IVA

Percent Released from 120 mg Pyridostigmine Br Extended Release Tablet Formulations[a]

	Percent Dissolved		
Time(hrs)	W-1-120[b]	W-2-120[b]	W-3-120[b]
0.5	22.5(2.8)[c]	36.1(0.9)[c]	47.5(8.5)[c]
1.0	31.6(4.6)	49.1(1.6)	76.2(10.7)
2.0	43.4(6.8)	65.7(2.3)	93.5(9.3)
4.0	53.6(1.4)	84.6(2.2)	103.4(5.5)
6.0	63.5(2.3)	94.1(0.4)	
8.0	71.2(3.1)	97.9(1.3)	
10.0	76.1(4.0)	100.3(0.5)	
12.0	82.0(3.5)		

[a]Normalized for theoretical content of 120 mg; Average of 2 tablets
[b]Formulation number
[c]Standard deviation

Table IVB

120 mg Pyridostigmine Br Extended Release Formulations

Component	W-1-120[d]	W-2-120[d]	W-3-120[d]
Pyridostigmine Br	120[e]	120[e]	120[e]
Castorwax®	500	250	-
PVP(K-30)	150	50	-
Mag. Stearate	10	5	1.25
Methocel® K15M	-	-	200
Dicalcium Phosphate	-	-	100
Avicel®	-	-	50
Cab-O-Sil®	-	-	0.75
Total Weight (mg)	780	425	472

[d]Formulation number
[e]Weight in milligrams

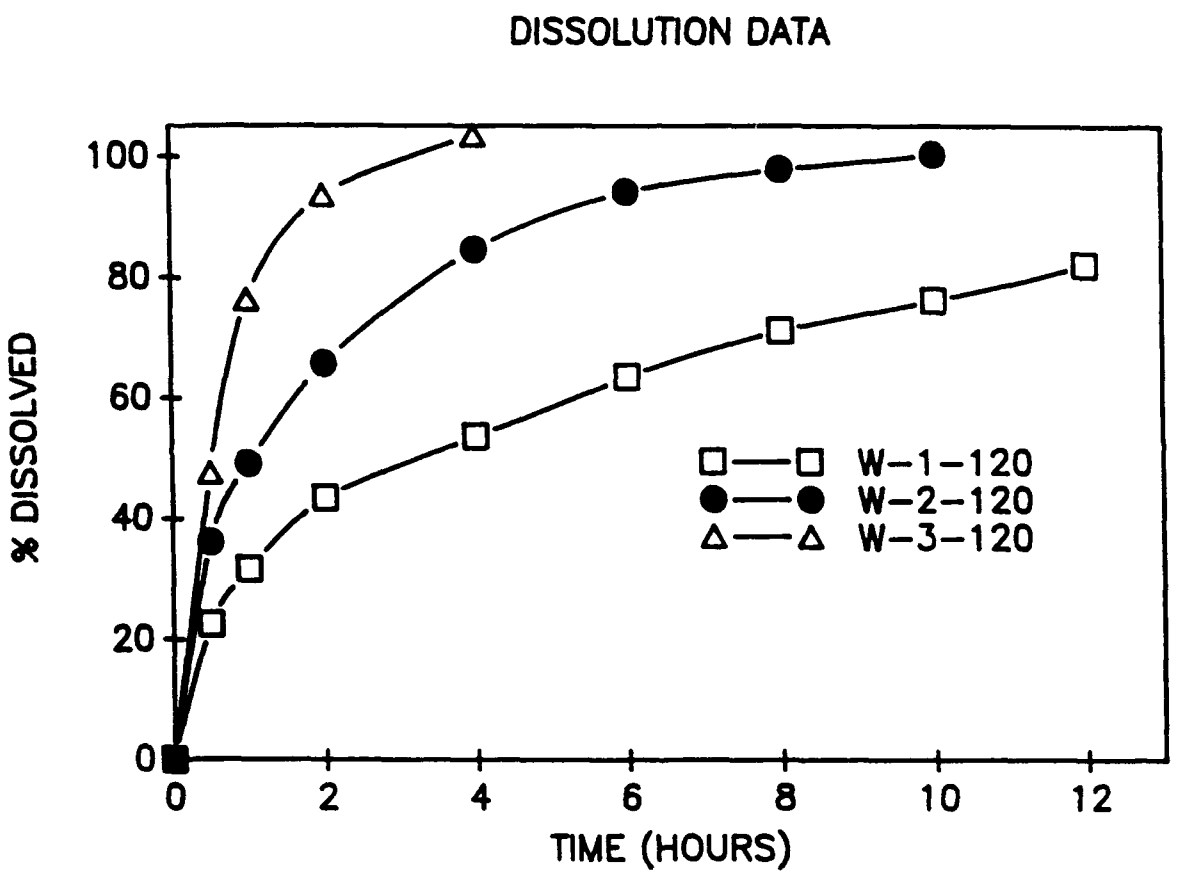

Figure 4. Release profiles from 120 mg extended release pyridostigmine Br tablets.

Table VA

Percent Released from 150 mg Pyridostigmine Br Extended Release Tablet Formulations[a]

	Percent Dissolved		
Time(hrs)	W-1-150[b]	W-2-150[b]	W-3-150[b]
0.5	24.3(1.0)[c]	45.1(1.1)[c]	34.7(2.0)[c]
1.0	31.8(1.5)	70.0(1.7)	44.4(1.4)
2.0	40.9(1.3)	83.8(1.7)	59.8(1.5)
4.0	53.6(1.3)	91.6(1.6)	78.4(2.0)
6.0	61.8(0.8)		90.4(0.3)
8.0	68.8(2.0)		
10.0	74.6(1.8)		
12.0	79.7(0.6)		

[a]Normalized for theoretical content of 150 mg; Average of 2 tablets
[b]Formulation number
[c]Standard deviation

Table VB

150 mg Pyridostigmine Br Extended Release Formulations

Component	W-1-150[d]	W-2-150[d]	W-3-150[d]
Pyridostigmine Br	150[e]	150[e]	150[e]
Castorwax®	500	-	250
PVP(K-30)	150	-	30
Mag. Stearate	10	1.25	5
Methocel® K15M	-	200	-
Dicalcium Phosphate	-	100	-
Avicel®	-	50	-
Cab-O-Sil®	-	0.75	-
Total Weight (mg)	810	502	435

[d]Formulation number
[e]Weight in milligrams

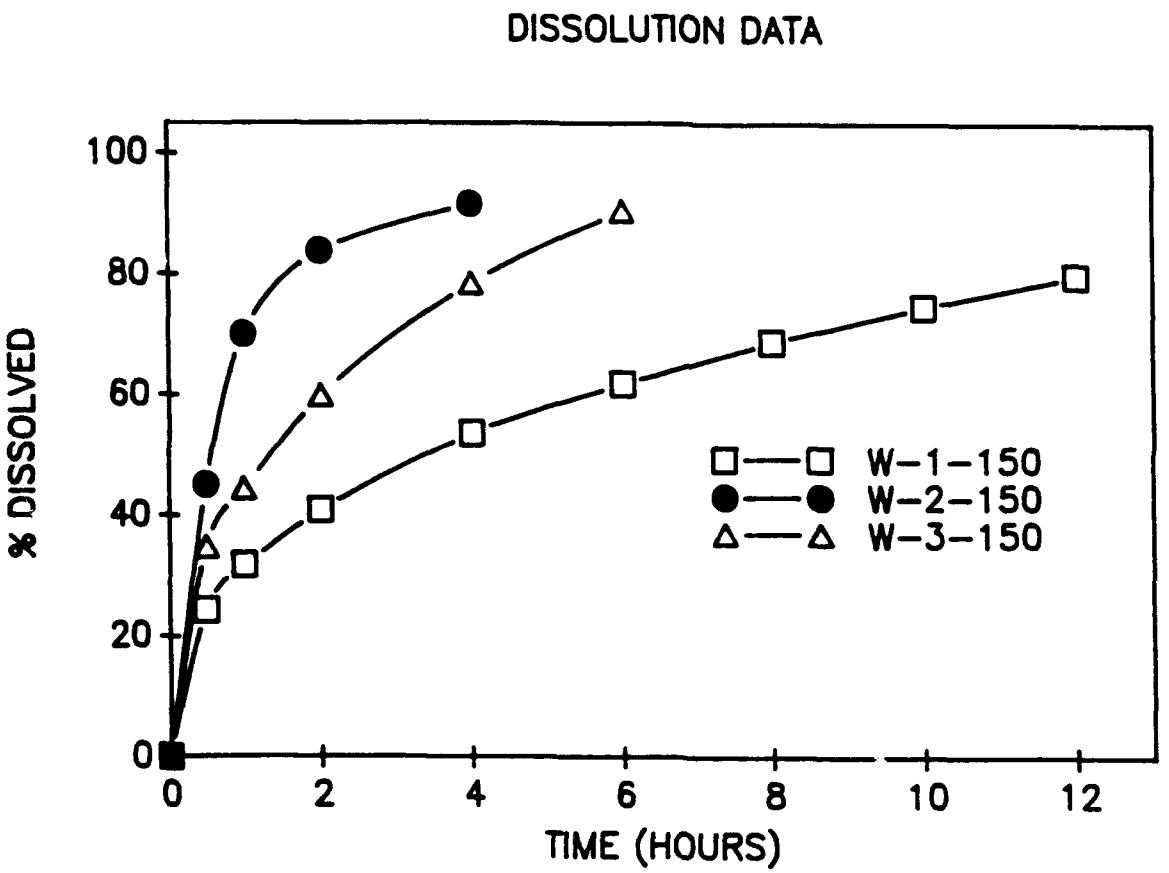

Figure 5. Release profiles from 150 mg extended release pyridostigmine Br tablets.

Conclusions

Sufficient 90 mg pyridostigmine formulations have been evaluated to select one of a number formulations that give good 6 hour and 12 hour release.

From the 120 mg and 150 mg formulations studied, it is possible to predict the release characteristics of further test formulations that would give more optimal 6 or 12 hour release. The particularly slow releasing W-1-120 and W-1-150 formulations would probably release faster *in vivo* because gastric fluids would better permeate the hydrophobic wax matrix than does the simulated gastric fluid used in the dissolution test.

Recommendations

If large quantities (i.e., >1000 tablets) of the best test formulations are required for human trials, more pyridostigmine will be required (2-3 kg) to perform adequate scale-up with these higher dose formulations. Also, it will require time (3-4 months) to prepare test batches on high speed production equipment and ensure they meet the usual compendial requirements and give the same release profiles as the individually prepared tablets.

If small quantities (i.e., 25-50 tablets) of the best test formulations are required for human trials, no additional pyridostigmine will be required. Scale-up problems could be avoided by preparing the tablets singly as was done for these test formulations. Such a production procedure would permit preparation of most test formulations in 30 days or less.

It is also recommended that these test formulations not be coated as previous formulations were. Coating adds further to the production time and sets a minimum batch size to be 1000-2000 tablets. If any formulations prove promising in limited human trials, scale-up and coating can be done with additional quantities of pyridostigmine and standard tablet production equipment.

Objective

The objective of this assignment was to formulate and produce a batch of pyridostigmine bromide extended release tablets in 90 mg strength. The tablets were formulated to release over approximately 6 hours. The tablets were coated with a hydroxypropyl methylcellulose/polyethylene glycol film coating.

Formulation and Production Methodology

Tablets containing the equivalent of 90 mg (1 batch) of pyridostigmine bromide were formulated and produced in a batch of approximately 2200 tablets. This tablet batch was formulated with hydroxypropylmethyl-cellulose (Methocel® K4M) and other excipients to give a release profile in which nearly complete in vitro release was achieved in approximately six hours.

Pyridostigmine bromide (WR #25710 AF, Bottle #BK75309) was used as received from WRAIR and its purity taken as 100% (data sheet cites 100.1%). The pyridostigmine bromide was stored in its original sealed containers under refrigeration until use and moisture uptake was checked by thermogravimetric analysis. No detectable moisture uptake was observed. Compendial identify tests were performed on pyridostigmine bromide and all excipients according to USP or NF specifications.

The following uncoated tablet formulation was produced in a batch size of approximately 2200 tablets:

	WRA-34-05099
Pyridostigmine Bromide	90 mg
Hydroxypropylmethyl-Cellulose (Methocel® K4M CR)	180 mg
Povidone (Plasdone® K29-32)	60 mg
Magnesium Stearate	3.3 mg
TOTAL TABLET WEIGHT (UNCOATED)	333.3 mg

Pyridostigmine bromide was blended with hydroxypropylmethylcellulose (Methocel® K4M CR) for 10 minutes in a V-blender. Povidone was added to this mixture and blended for a further 10 minutes. The powder blend was wetted with approximately 200 ml of 95% ethanol and passed through a 10-mesh sieve. The wet granulation was dried overnight at ambient temperature. The dried granulation was passed through a 20-mesh sieve. Magnesium stearate was added to the granulation and blended for 5 minutes. Samples (3) were taken from each side and the center of the blender and assayed for content uniformity.

The tablets (677 gm) were produced on a Manesty single station tablet machine with 7/16 inch standard concave punches. Tablet weights were monitored throughout the production run to insure uniformity of tablet

weight. Tablet hardness was measured with a Schleuniger hardness tester. This tablet formulation gave hardness values around 4-5 kp (uncoated) and 10-12 kp (coated).

The tablets (510 gm) were coated with a hydroalcoholic film coating solution in a Freund Mini Hi-Coater HCT-20. The coating solution contained 10% hydroxypropyl methylcellulose #2910, USP, 6 cps (Shin-Etsu Pharmacoat 606) and 1% polyethylene glycol 3350, NF (Ruger) in a hydroalcoholic solution. Opaspray K-1-7000 was suspended in the coating solution to produce a white opaque coat.

Packaging

Twenty tablets were counted into 7 dram amber glass vials. A dessicant pack (0.50 gm) was placed in each vial to reduce moisture absorption by the hygroscopic pyridostigmine bromide and hydroxypropyl methylcellulose. The void space in each vial was filled with rayon pharmaceutical coil. The vials were sealed with white phenolic caps and a Halpak® PVC shrink seals (50 mm x 25 mm) were placed over each cap.

Labels

Labels were prepared to include drug name, dose, # of tablets/vials, Lot # (Control No.), manufacturing date, an individual bottle # (1-67) and the designation, "Extended Release Tablets." Additional information identifies Pharmaceutical Service of the University of Iowa as manufacturer and Walter Reed Army Institute of Research.

USP Tests

The weight variation test for uncoated tablets was conducted on 20 tablets according to the procedure in USP XX, p. 990 (Note-USP XXI, p. 1277 indicates a weight variation test that is dependent on specific monograph requirements). The following weight variation results were obtained on 20 uncoated tablets:

	WRA-34-05099
Average Weight (mg)	337.44
Std. Dev. (mg)	4.89
Rel. Std. Dev. (%)	1.45

All weight variation falls within 5% of the average.

The content uniformity test for coated tablets was conducted for ten tablets as described in USP XXI, pp 1277-1278. The assays were conducted on individual coated tablets by the attached procedure. Below are the results of the content uniformity tests on 10 coated tablets:

	WRA-34-05099
Average Content (mg)	89.11
Std. Dev. (mg)	1.79
Rel. Std. Dev. (%)	2.00

Objective

The objective of this work is to formulate and produce capsules of WR6026•2HCl, an experimental antileishmanial drug, for use in human trials.

Summary

Capsules of WR6026•2HCl (5 and 15 mg), and matching placebo capsules were formulated and produced. The basic formulation for the drug-containing capsule utilized the deposition of dissolved WR6026•2HCl onto hydrous lactose, NF, from a solution of drug in absolute ethanol, USP. The placebo formulation was produced using a dry blend procedure with hydrous lactose, NF, and colloidal silicon dioxide as excipients. For color matching purposes, D&C Yellow #10 lake was added to the placebo formulation instead of the WR6026•2HCl. The formulations were encapsulated into #2 white opaque gelatin capsule shells.

The disintegration test for all lots demonstrated capsule opening in less than 3 minutes at 37°C in 900 ml of distilled water.

The content uniformity based on UV analysis of 10 capsules of the five mg capsule (Lot WRA-040-07179) formulation yielded an average of 98.2% of label claim with a range of 94.5% to 103.7%. For ten 15 mg capsules (lot WRA-041-07189) the average content uniformity based on UV analysis was 101.9% of label claim with a range of 98.8% to 106.9%.

The weight variation test for twenty placebo capsules (Lot 07199) showed an average fill of 332.1 mg per capsule with a range of 307.8 to 353.0 mg. In all cases the balance was tared with an empty capsule shell.

In all lots USP requirements were met for weight variation, content uniformity and disintegration.

Methodology

WR6026•2HCl (Lot AF) was used as received frm WRAIR. The drug was stored in the original amber glass container at room temperature until use.

Purity

The purity of the drug was taken as 99.5% as reported by SRI Analysis Report No. 394. Purity was reported in SRI Report No. 534(1).

Formulation Ingredients

Identification tests were carried out on the formulation excipients (i.e., hydrous lactose, NF, colloidal silicon dioxide, NF, absolute ethyl alcohol, USP) according to compendial requirements. WR6026-2HCl (Lot AF) was identified by comparing its ultraviolet spectrum and molar absorbtivity at selected wavelengths in aqueous solution with that reported previously (2). The coloring agent, D&C yellow #10 lake, used for the placebos was identified by comparing its solution spectrum to that obtained from previous lots of the same material.

Manufacturing Procedure

The 5 mg formulation (WRA-040-07179) was produced by dissolving 12.875 gm of WR6026•2HCl in 250 ml of absolute ethyl alcohol, USP. Hydrous lactose, NF (822 gm) was added to a stainless steel mixing bowl and the alcoholic drug solution added. Two 50 ml portions of absolute alcohol were used to rinse the beaker containing the drug solution. The drug-alcohol-lactose slurry was slowly mixed until the alcohol had largely evaporated, leaving the drug deposited on the lactose. The granulation was passed through a #20 mesh screen and tray dried at room temperature for 12 hours. The dried granulation was sized by passing through a #30 mesh screen and added to a 2 quart plexiglas V-blender shell. A small quantity of colloidal silicon dioxide (3.0 gm) was added. Blending was carried out for 10 minutes. No. 2 white opaque gelatin capsules were filled with 335 mg of powder blend using a Parke Davis #9 capsule filling machine.

The 15 mg formulation (#WRA-041-07189) was produced by dissolving 38.625 gm of WR6026•2HCl in 850 ml of absolute ethyl alcohol, USP. Hydrous lactose, NF (822 gm) was added to a stainless steel mixing bowl and the alcoholic drug solution added. Two 50 ml portions of absolute alcohol were used to rinse the beaker containing the drug solution. The drug-alcohol-lactose slurry was slowly mixed until the alcohol had largely evaporated, leaving the drug deposited on the lactose. The granulation was passed through a #20 mesh screen and tray dried at room temperature for 12 hours. The dried granulation was sized by passing through a #30 mesh screen and added to a 2 quart plexiglas V-blender shell. A small quantity of colloidal silicon dioxide (3.0 gm) was added. Blending is carried out for 10 minutes. No. 2 white opaque gelatin capsules were filled with 345.3 mg of powder blend using a Parke Davis #9 capsule filling machine.

The placebo formulation (WRA-042-07199) was produced by mixing 1,312 gm of hydrous lactose, NF, 11.2 gm of D&C Yellow #10 Lake and 4.8 gm of colloidal silicon dioxide, NF, in a one quart V-blender shell for 10 minutes. No. 2 white, opaque gelatin capsules were filled with 332 mg of powder blend using a Parke Davis #9 Capsule Filling machine.

USP Method and Requirements

The weight variation test for capsules is described on pp. 1617-1618 of USP XXII. Capsules must be weighed individually and the individual weights should be within the limits of 90 to 110% of the average weight. This test was conducted only on placebo capsules according to the USP requirements. The USP XIX specification was used for placebo capsule weight variation because it was based on weight and not referred to an assay value. It is not necessary to perform weight variation testing of lots of capsules for which content uniformity testing is carried out.

The disintegration test is described on pp. 1577-1578 of USP XXII. Six capsules from each capsule batch were tested with 900 cc of water at 37°C as the disintegration medium using the standard basket-rack assembly described in USP XXII.

The content uniformity test for capsules is described on pp. 1617-1618 of USP XXII. At least ten capsules of each capsule batch were assayed individually by a UV spectral analysis (2). Ten capsules of each batch were assayed individually and the content of each of not less than nine capsules were required to be within the limits of 85 to 115% of the label claim with a relative standard deviation of less than 6.0%.

No dissolution test was performed on the capsules because of the high solubility of WR6026•2HCl (i.e., > 200 mg/ml). Compendial dissolution tests are only required for drugs or drug formulations which have poor solubility which could result in poor dissolution characteristics.

Results

Disintegration Test

For all lots the disintegration time was less than 3 minutes.

Weight Variation Test

The weight variation test for twenty placebo capsules (Lot WRA-042-07199) produced an average fill of 332.1 mg per capsule with a fill range of 307.8 to 341.4 mg.

Content Uniformity Test

The content uniformity test of 10 capsules of the five mg capsule (Lot WRA-040-07179) formulation yielded an average of 98.2% of label claim with a range of 94.5% to 103.7%. For ten 15 mg capsules (Lot WRA-041-07189) the average content uniformity was 101.9% of label claim with a range of 98.8% to 106.7%

Batch Size

The number of 5 mg capsules filled in Lot WRA-040-07179 was 2534 capsules. The number of 15 mg capsules filled in Lot WRA-041-07189 was 2422 capsules. The number of placebo capsules filled in Lot WRA-042-07199 was 3782.

Packaging

Twenty capsules each were placed into 7 dram glass amber vials. The void space was filled with pharmaceutical rayon coil and sealed with standard closures.

Labels

Labels were prepared as per instructions.

Conclusions

The capsule formulations of WR6026•2HCl meet all compendial requirements for capsules and are similar to those prepared in previous production batches.

References

1. Lim, P., et al., Report No. 534, April 1986, Contract No. DAMD 17-85-C-5141, SRI International, 333 Ravenswood Avenue, Menlo Park, California, 94025.

2. Lach, J. L., et al., Annual Report No. 2, July 1981, Contract No. DAMD 17-79-C-9136, College of Pharmacy, University of Iowa, Iowa City, Iowa, 52242.

3. Lach, J. L., et al., Study Report No. 22, June 1986, Contract No. DAMD 17-85-C-5003, College of Pharmacy University of Iowa, Iowa City, Iowa, 52242.

Objective

The objective of this work is to formulate and produce capsules of 2 dose levels of WR238,605, an experimental antimalarial drug, and a placebo for use in human trials.

Summary

Capsules of WR238,605 (15 and 5 mg), and matching placebo capsules were formulated and produced. The basic formulation for the drug-containing capsule involved mixing WR238,605 with lactose and microcrystallinesilica (Cab-O-Sil). The placebo formulation was produced using only powdered lactose, NF. The formulations were encapsulated into #2 white opaque gelatin capsule shells.

The disintegration test for all lots demonstrated capsule opening in less than 4 minutes at 37°C in 900 ml of distilled water.

The content uniformity based on UV analysis of 10 capsules of the 15 mg capsule (Lot WRA-046-01076) formulation yielded an average of 105.1% of label claim with a range of 102.3% to 110.8%. For ten 5 mg capsules (Lot WRA-043-06180) the average content uniformity based on UV analysis was 98.3% of label claim with a range of 90.8% to 108.9%.

The weight variation test for twenty placebo capsules (Lot WRA-045-06200) showed an average fill of 316.9 mg per capsule with a range of 284.4 to 332.6 mg. In all cases the balance was tared with an empty capsule shell.

In all lots USP requirements were met for weight variation, content uniformity and disintegration.

Methodology

WR238,605 (Lots AC and AP-10-230) was used as received from WRAIR. The drug was stored in the original amber glass container at room temperature until use.

Purity

The purity of the drug was taken as 100% for manufacturing purposes.

Formulation Ingredients

Identification tests were carried out on the formulation excipients (i.e., hydrous lactose, NF, colloidal silicon dioxide, NF, absolute ethyl alcohol, USP) according to compendial requirements. WR6026-2HC1 (Lot AF) was identified by comparing its ultraviolet spectrum and molar absorptivity at selected wavelengths in aqueous solution with that reported previously (2). The coloring agent, D&C yellow #10 Lake, used for the placebos was identified by comparing its solution spectrum to that obtained from previous lots of the same material.

Manufacturing Procedure

The 5 mg formulation (WRA-040-07179) was produced by dissolving 12.875 gm of WR6026•2HCl in 250 ml of absolute ethyl alcohol, USP. Hydrous lactose , NF (822 gm) was added to a stainless steel mixing bowl and the alcoholic drug solution added. Two 50 ml portions of absolute alcohol were used to rinse the beaker containing the drug solution. The drug-alcohol-lactose slurry was slowly mixed until the alcohol had largely evaporated, leaving the drug deposited on the lactose. The granulation was passed through a #20 mesh screen and tray dried at room temperature for 12 hours. The dried granulation was sized by passing through a #30 mesh screen and added to a 2 quart plexiglas V-blender shell. A small quantity of colloidal silicon dioxide (3.0 gm) was added. Blending was carried out for 10 minutes. No. 2 white opaque gelatin capsules were filled with 335 mg of powder blend using a Parke Davis #9 capsule filling machine.

The 15 mg formulation (#WRA-041-07189) was produced by dissolving 38.625 gm of WR6026•2HCl in 850 ml of absolute ethyl alcohol, USP. Hydrous lactose, NF (822 gm) was added to a stainless steel mixing bowl and the alcoholic drug solution added. Two 50 ml portions of absolute alcohol were used to rinse the beaker containing the drug solution. The drug-alcohol-lactose slurry was slowly mixed until the alcohol had largely evaporated, leaving the drug deposited on the lactose. The granulation was passed through a #20 mesh screen and tray dried at room temperature for 12 hours. The dried granulation was sized by passing through a #30 mesh screen and added to a 2 quart plexiglas V-blender shell. A small quantity of colloidal silicon dioxide (3.0 gm) was added. Blending is carried out for 10 minutes. No. 2 white opaque gelatin capsules were filled with 345.3 mg of powder blend using a Parke Davis #9 capsule filling machine.

The placebo formulation (WRA-042-07199) was produced by mixing 1,312 gm of hydrous lactose, NF, 11.2 gm of D&C Yellow #10 Lake and 4.8 gm of colloidal silicon dioxide, NF, in a one quart V-blender shell for 10 minutes. No. 2 white, opaque gelatin capsules were filled with 332 mg of powder blend using a Parke Davis #9 Capsule Filling machine.

USP Method and Requirements

The weight variation test for capsules is described on pp. 1617-1618 of USP XXII. Capsules must be weighed individually and the individual weights should be within the limits of 90 to 110% of the average weight. This test was conducted only on placebo capsules according to the USP requirements. The USP XIX specification was used for placebo capsule weight variation because it was based on weight and not referred to an assay value. It is not necessary to perform weight variation testing of lots of capsules for which content uniformity testing is carried out.

The disintegration test is described on pp. 1577-1578 of USP XXII. Six capsules from each capsule batch were tested with 900 cc of water at 37°C as the disintegration medium using the standard basket-rack assembly described in USP XXII.

The content uniformity test for capsules is described on pp. 1617-1618 of USP XXII. At least ten capsules of each capsule batch were assayed individually by a UV spectral analysis (2). Ten capsules of each batch were assayed individually and the content of each of not less than nine capsules were required to be within the limits of 85 to 115% of the label claim with a relative standard deviation of less than 6.0%.

No dissolution test was performed on the capsules because of the high solubility of WR6026•2HCl (i.e., > 200 mg/ml). Compendial dissolution tests are only required for drugs or drug formulations which have poor solubility which could result in poor dissolution characteristics.

Results

Disintegration Test

For all lots the disintegration time was less than 3 minutes.

Weight Variation Test

The weight variation test for twenty placebo capsules (Lot WRA-042-07199) produced an average fill of 332.1 mg per capsule with a fill range of 307.8 to 341.4 mg.

Content Uniformity Test

The content uniformity test of 10 capsules of the five mg capsule (Lot WRA-040-07179) formulation yielded an average of 98.2% of label claim with a range of 94.5% to 103.7%. For ten 15 mg capsules (Lot WRA-041-07189) the average content uniformity was 101.9% of label claim with a range of 98.8% to 106.7%.

Batch Size

The number of 5 mg capsules filled in Lot WRA-040-07179 was 2534 capsules. The number of 15 mg capsules filled in Lot WRA-041-07189 was 2422 capsules. The number of placebo capsules filled in Lot WRA-042-07199 was 3782.

Packaging

Twenty capsules each were placed into 7 dra glass amber vials. The void space was filled with pharmaceutical rayon coil and sealed with standard closures.

Labels

Labels were prepared as per instructions.

Conclusions

The capsule formulations of WR6026•2HCl meet all compendial requirements for capsules and are similar to those prepared in previous production batches.

References

1. Lim, P., et al., Report No. 534, April 1986, Contract No. DAMD 17-85-C-5141, SRI International, 333 Ravenswood Avenue, Menlo Park, California, 94025.

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